PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference CJG/PB60825	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2005/001333	International filing date *(day/month/year)* 06.04.2005	Priority date *(day/month/year)* 08.04.2004
International Patent Classification (IPC) or national classification and IPC INV. C07D403/14 C07D223/16 C07D401/12 C07D401/14 C07D413/14 C07D403/12 A61K31/55 A61P25/00		
Applicant GLAXO GROUP LIMITED et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 1 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18.11.2005	04.08.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Weisbrod, T Telephone No. +49 89 2399-8931

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2005/001333

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:

   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-36	as originally filed

Claims, Numbers

1(part), 2-9	as originally filed
1(part)	received on 21.11.2005 with letter of 16.11.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 7

because:

☒ the said international application, or the said claims Nos. 7 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☐ no international search report has been established for the said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2005/001333

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2
	No:	Claims	1,3-9
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-9
Industrial applicability (IA)	Yes:	Claims	1-6,8,9
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item I

Basis of the opinion

With his letter of 16.11.2005 the applicant filed an amended part of claim 1, wherein X has been limited to a bond and methyl (before a bond and C_{1-6}alkyl). The amendment complies with Article 19(2) and 34(2)(b) PCT.

The application is directed to
(i) tetrahydrobenzo[d]azepines (I) (claims 1-2),
(ii) a pharmaceutical composition with a compound (I) (claim 3),
(iii) the medical use of compounds (I) (claims 4-6),
(iv) the corresponding therapeutic method (claim 7),
(v) the medical use of the pharmaceutical composition (claim 8), and
(vi) a process for the preparation of compounds (I) (claim 9).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 7 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents.

D1: WO 2004/018432, 4 March 2004; cited in the application.
D2: WO 2004/026305, 1 April 2004; cited in the application.
D3: WO 2004/035544, 29 April 2004.
D4: WO 20047056369, 8 July 2004.
D5: WO 2005/014479, 17 February 2005.
D6: WO 2005/039591, 6 May 2005.

D3 to **D6** were published after the priority date. Under the presumption that the priority is valid for the claimed matter these documents are not considered as prior

art under Rule 64.1 PCT.

2 Novelty

The application does not comply with the criterion of novelty for the following reasons.

2.1 **D1** discloses histamine H_3 receptor antagonists, from which the present compounds (I) differ through R^2 (present R^2 = e.g. -X-heterocyclyl with X = bond or methyl; corresponding group in D2: C_{2-5}alkylene-piperidin-1-yl or C_{2-5}alkylene-pyrrolidin-1-yl). Hence, the present claimed matter is novel vis-à-vis **D1**.

D2 discloses opioid receptor antagonists, their preparation, a pharmaceutical composition comprising them, and their medical use in the treatment of neurological disorders such obesity-related depression or anxiety, and stroke (cf. claim 30). The compounds of **D2** overlap with the present compounds (I) when R^1 is optionally substituted C_{2-7}alkyl or C_{3-7}cycloalkyl and R^2 is $CONR^5R^6$-substituted -X-aryl or -X-heteroaryl with X being a bond (cf. **D2**, claim 1, wherein ring A is a benzene ring; $(CR^3R^{3'})_v$ is $-CH_2-CH_2-$; R^2 is C_2alkyl attached to ring A to form a 7-membered nitrogen-containing bicyclic heterocycle; R^1 is C_{1-8}alkyl, C_{3-8}cycloalkyl, -C_{1-8}alkyl-C(O)-C_{1-8}alkyl, C_{1-8}alkoxy-C_{1-8}alkyl, $-(CH_2)_nC(O)R^8$; and ring B is phenyl, pyridyl or a diazine ring). In addition, the document discloses already one specific embodiment within the overlapping range and its preparation according to process (a) of present claim 9 (cf. page 226, step 8: present compound (I) with R^1 = C_2alkyl substituted with one oxo group and three fluoro groups; R^2 = X-heteroaryl with X = bond; and heteroaryl is substituted with $CONR^5R^6$, R^5 = R^6 = H, n = 0). Hence, the present claims 1 and 3-9 lack novelty in view of **D2**.

2.2 **D3** discloses histamine H_3 receptor antagonists and reverse agonists (page 7, lines 26-35) according to the present formula (I) wherein R^1 is C_{2-6}alkyl or $-(CH_2)_m$-C_{3-7}cycloalkyl and R^2 is -X-heterocyclyl (cf. claim 1; and e.g. examples E2, E12, E18, E29, E30, E48 for specific embodiments within the overlapping range).

D4 shows further H_3 receptor antagonists and reverse agonists (page 14, lines 12-21) of the present formula (I) wherein R^1 is C_{3-7}cycloalkyl and R^2 is as in the present application (cf. claim 1 and the examples e.g. E1, E2, etc.).

D5 relates to a process for the preparation of radiolabelled compounds. In this context the document discloses two compounds of the present formula (I) (cf. page 17, structural formulae).

D6, finally, discloses MAO-B inhibitors of the present formula (I) wherein R^1 is optionally substituted C_{2-3} alkyl and R^2 is $-CH_2$-(optionally substituted phenyl) (cf. claim 1, $R^2 = C_{1-3}$alkyl, $C(O)R^6$; $R^6 = -CH_3$, $-CH_2OCH_3$; and e.g. example 1 for a specific embodiment within the overlapping range).

D3 to **D6** are likely to become relevant to the question of novelty of present claims in the regional phase.

3 Inventive Step and Unity of Invention

Insofar as the application relates to novel compounds (I) the following observation would apply to the requirements of inventive step and unity of invention.

3.1 The application describes the preparation of certain compounds (I) and shows that such compounds act as histamine H_3 receptor antagonists (the application, page 36).

3.2 **D1** discloses already histamine H_3 receptor antagonists from which the present compounds (I) differ through R^2. Starting from **D1** as most relevant state of the art, the problem underlying the application may be seen in the provision of further histamine H_3 receptor antagonists. In view of the very close structural relationship of certain present compounds (I) and those of **D1**, the present compounds (I) appear to represent merely obvious alternatives of the compounds of **D1**. Hence, in the absence of any substantiated unexpected effect(s) of the present compounds (I) compared with the respective structurally closest related compounds of **D1**, no inventive activity would be seen in the claimed subject matter.

In addition, the terms "aryl", "heteroaryl", and "heterocyclyl" used in claim 1 are open-ended and thus likely to comprise structures which will not solve any relevant technical problem. Thus, no inventive step would be acknowledged for open-ended compounds (I) and subject-matter referring to them.

Therefore, the claims 1-9 do not meet the requirements of inventive step.

4 Industrial Applicability

For the assessment of the present claim 7 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the

use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 2004/035544 A1	29.04.2004	14.10.2003	16.10.2002
WO 20047056369 A1	08.07.2004	18.12.2003	20.12.2002
WO 2005/014479 A2	17.02.2005	05.08.2004	08.08.2003

Re Item VIII

Certain observations on the international application

The application does not comply with the requirements of Article 6 PCT for the following reasons.

1 Claim 2 is to be objected under Article 6 in combination with Rule 6.2(a) PCT for referring to the examples in the description.

2 Claim 9 is directed to a process for the preparation of compounds (I) comprising five process steps (a) to (e). However, it is not apparent how compounds (III) defined in process step (b) are accessible from compounds (II) of process step (a) wherein R^1 is different from hydrogen. In addition, process step (d) refers to "compound of formula (I) which is protected". However, none of the current claims gives any indication of the formula of such "protected compound (I)", thereby resulting in a lack of clarity of the claim.